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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 471/04	A1	(11) International Publication Number: WO 97/44342
		(43) International Publication Date: 27 November 1997 (27.11.97)

(21) International Application Number: PCT/KR97/00074

(22) International Filing Date: 2 May 1997 (02.05.97)

(30) Priority Data:
1996/16624 17 May 1996 (17.05.96) KR

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(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: PROCESS FOR PREPARING 1-ARYL-4-OXOPYRROLO[3,2-c]QUINOLINE DERIVATIVES

(57) Abstract

The present invention relates to a process for preparing 1-aryl-4-oxopyrrolo[3,2-c]quinoline derivatives through reaction of 4-oxofuro[3,2-c]quinoline compounds with aniline compounds under mild conditions in a single step, wherein 1-aryl-4-oxopyrrolo[3,2-c]quinoline derivatives having various substituents may be prepared in high yield, so that the 1-aryl-4-oxopyrrolo[3,2-c]quinoline derivatives may be utilized as an intermediate for producing a reversible inhibitor of gastric acid secretion.

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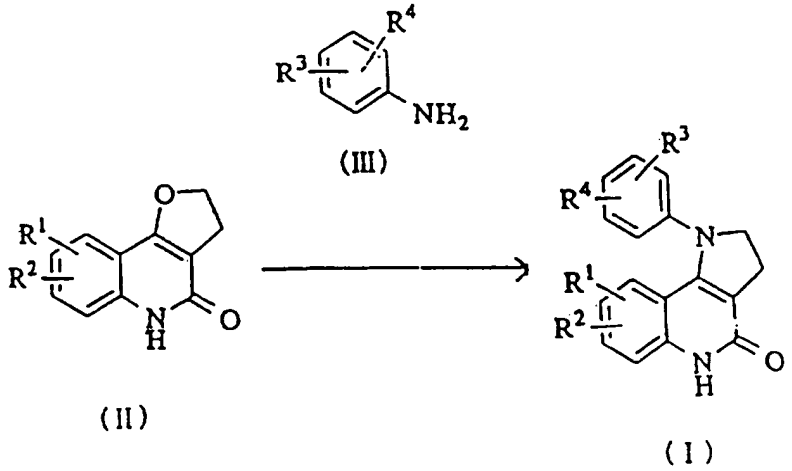
PROCESS FOR PREPARING 1-ARYL-4-OXOPYRROLO[3,2-c]QUINOLINE DERIVATIVES

Field of the invention

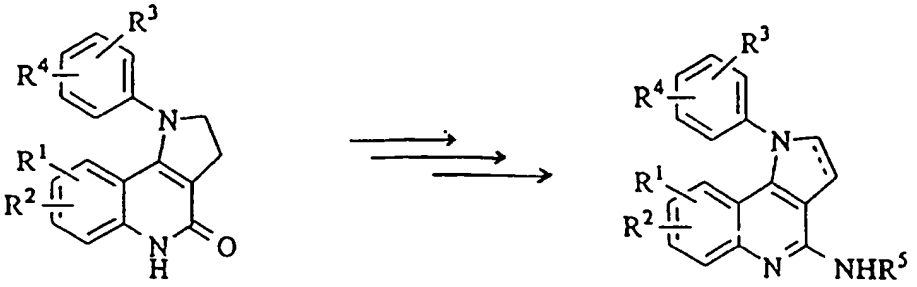
The present invention relates to a process for preparing 1-aryl-4-oxopyrrolo[3,2-c]quinoline derivatives and, more particularly, to a process for preparing 1-aryl-4-oxopyrrolo[3,2-c]quinoline derivatives represented by structure I which is prepared through the reaction of 4-oxofuro[3,2-c] quinolines with anilines represented by structure III. The formulae I, II and III are as follows:



wherein, R^1 may be same or different from R^2 which are respectively hydrogen, lower alkyl group of C_1-C_4, lower alkoxy group of C_1-C_4, lower alkylthio group of C_1-C_4, lower haloalkoxy group of C_1-C_4, trifluoromethyl group, hydroxyalkoxy group of C_1-C_4, halogen, or hydroxy group; and

R^3 may be same or different from R_4 which are respectively hydrogen, lower alkyl group of C_1-C_4, lower alkoxy group of C_1-C_4, lower alkylthio group of C_1-C_4, lower haloalkyl group of C_1-C_4, trifluoromethyl group, hydroxy group, amino group, or halogen.

The 1-aryl-4-oxopyrrolo[3,2-c]quinoline derivatives which are prepared according to the present invention are used as intermediates for preparing compounds as represented by structure IV for suppressing gastric acid secretion and many studies have been carried out to prepare the intermediate so far [European Patent Application No. 90-313398.1; European Patent Application No. 88-306583.1; J. Med. Chem., 1990, 33, 527; J. Med. Chem., 1992, 35, 1845].



(I) (IV)

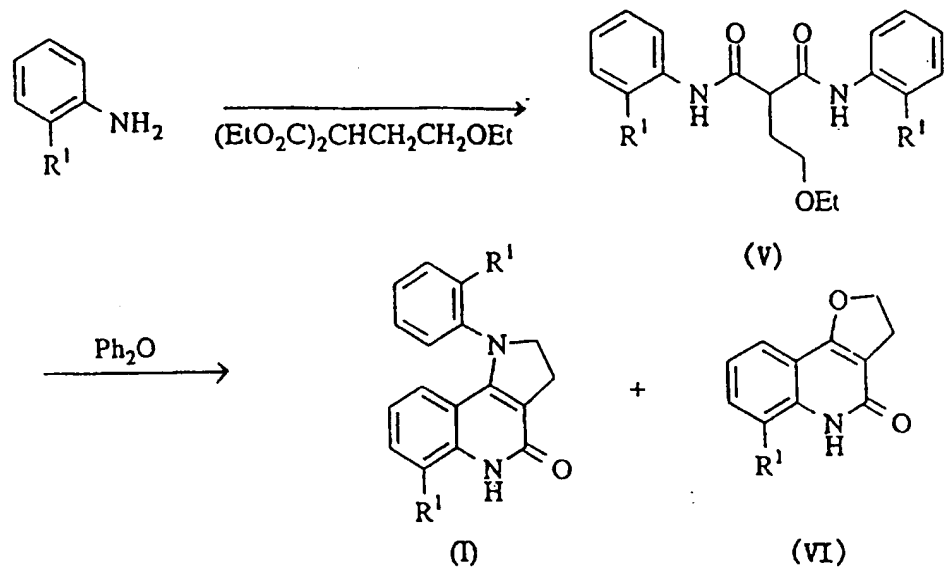
The present invention is to provide a process for preparing compounds as represented by the above structure I which are intermediates in preparation of compounds as represented by the above structure IV which are useful as repressor of the gastric acid secretion.

The present invention is to provide a process for preparing compounds as represented by the above formula IV by using the 1-aryl-4-oxopyrrolo[3,2-c] quinoline derivatives which can be prepared in a single reaction step from 4-oxofuro[3,2-c]quinoline with anilines III.

Prior Art

European Patent Application No. 88-306583.1 and an article [J. Med. Chem., 1992, 35, 1845] disclose a process for preparing 1-aryl-4-oxopyrrolo[3,2-c]

quinoline derivatives as represented by the above structure I, which may be summarized as follows:

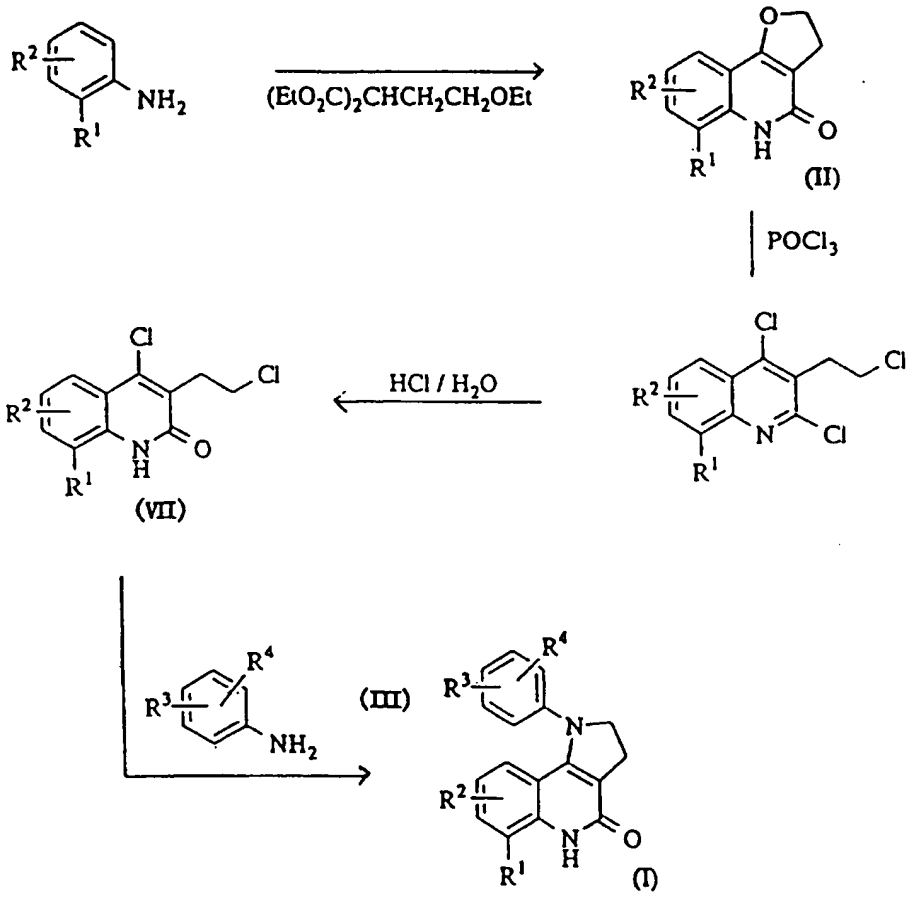


According to the prior art, the 1-aryl-4-oxo pyrrolo[3,2-c]quinoline derivatives I is prepared through reaction of $(EtO_2C)_2CHCH_2CH_2OEt$ with anilines as starting material.

This method has, however, disadvantages that yield is low while producing the compound I and a large amount of the compounds VI is formed as a by-product.

Further, the method has an inherent limitation that substituents are limited to R^1 initially present in the starting anilines, and it is impossible to prepare derivatives which has variable substituents.

On the other hand, an article [J. Med. Chem., 1992, 35, 1845] discloses a process for preparing compounds I having substituents R^1, R^2, R^3 and R^4, which may be summarized as follows:



According to the above method, 4-oxofuro[3,2-c] quinolines are chlorinated with $POCl_3$ and subject to hydrolysis to obtain compounds VII, so that 1-aryl-4-

oxopyrrolo[3,2-c]quinoline derivatives I having the substituents R^1, R^2, R^3 and R^4 through the reaction of various anilines with the compounds VII.

The method has still disadvantages that a great amount of very toxic $POCl_3$ has to be used as a reaction reagent and yields are relatively low about 50-70% in each reaction steps. Further, the compound I was obtained in mere prepared 20% yield due to the rather lengthy reaction steps from the compound II.

Therefore, the present inventors have developed a novel process to resolve the disadvantages of prior art and to prepare the compounds IV with high biological activity and various substituents through environmentally friendly and simple steps.

As a result, the quinoline compound IV may be prepared in a high yield by using 1-aryl-4-oxopyrrolo [3,2-c]quinoline derivatives which may be prepared conveniently in a high yield in such a manner that 4-oxofuro[3,2-c]quinolines II as starting material are reacted with various anilines as reactant in a single step.

SUMMARY OF THE INVENTION

The present invention has an objective to

provide a process for preparing 1-aryl-4-oxopyrrolo [3,2-c]quinoline derivatives I through a single step to react 4-oxofuro[3,2-c]quinolines II as a starting material with aniline III.

The present invention has another objective to provide a process for preparing quinoline compounds IV by using the 1-aryl-4-oxopyrrolo[3,2-c]quinoline derivatives.

According to the present invention, the above objective can be achieved by a process for preparing 1-aryl-4-oxopyrrolo[3,2-c]quinoline derivatives by reacting 4-oxofuro[3,2-c]quinolines with anilines under a gentle condition in a single step, wherein 1-aryl-4-oxopyrrolo[3,2 -c]quinoline derivatives having various substituents may be obtained in high yield, so that the 1-aryl-4-oxopyrrolo[3,2-c]quinoline derivatives may be utilized as intermediate for producing a reversible inhibitor of gastric acid secretion.

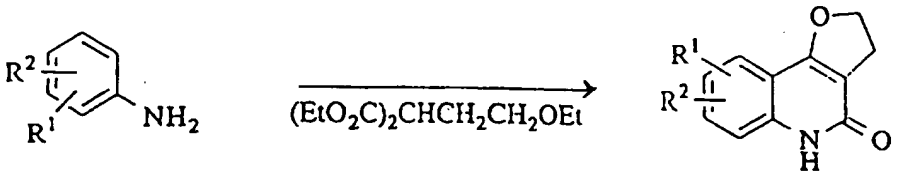
DETAILED DESCRIPTION OF THE INVENTION

The present invention will now be described in detail with reference to the schemes showing embodiments thereof.

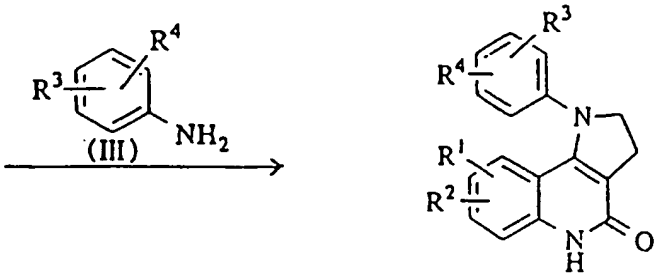
The present invention relates to a method of

preparing 1-aryl-4-oxopyrrolo[3,2-c]quinoline derivatives represented by structure I which are useful intermediate for compounds represented by structure IV with high biological activity, wherein the 1-aryl-4-oxopyrrolo[3,2-c]quinoline derivatives are prepared by the reaction of aniline compounds represented by structure III with 4-oxofuro[3,2-c]quinolines represented by structure II as starting material.

According to the present invention, the 1-aryl-4-oxopyrrolo[3,2-c]quinoline derivatives with various substituents R^1, R^2, R^3 and R^4 may be prepared in higher than 70% of yield.



(II)



(I)

In the formulae I, II and III, substituents R^1,

R^2, R^3 and R^4 are defined as above.

The preparation of substituted quinoline compounds, 4-oxofuro[3,2-c]quinoline derivatives II used as starting material are well described in the prior art [1, J. Chem. Sec., 1955, 4284; 2. J. Med. Chem., 1992, 35, 1845].

According to the present invention, solvent is selected from those such as dimethylformamide, dimethyl sulfoxide, diphenyl ether, xylene and the like, or alcoholic solvents such as butyl alcohol, phenol, ethylene glycol monomethyl ether and the like. Preferably, the solvent is selected from alcoholic solvents of which boiling point is 150-280°C, such as phenol, ethylene glycol, diethylene glycol or polyethylene glycol.

The process for preparing 1-aryl-4-oxopyrrolo [3,2-c]quinoline derivatives according to the present invention is preferably performed under inert atmosphere, such as argon or nitrogen.

As a reaction catalyst, p-toluenesulfonic acid and p-toluenesulfonic acid pyridine salt (PPTS) may be used.

Reaction temperature is preferably maintained at 70-300°C, and more preferably, 150-280°C, and reaction time is preferably 7-20 hours.

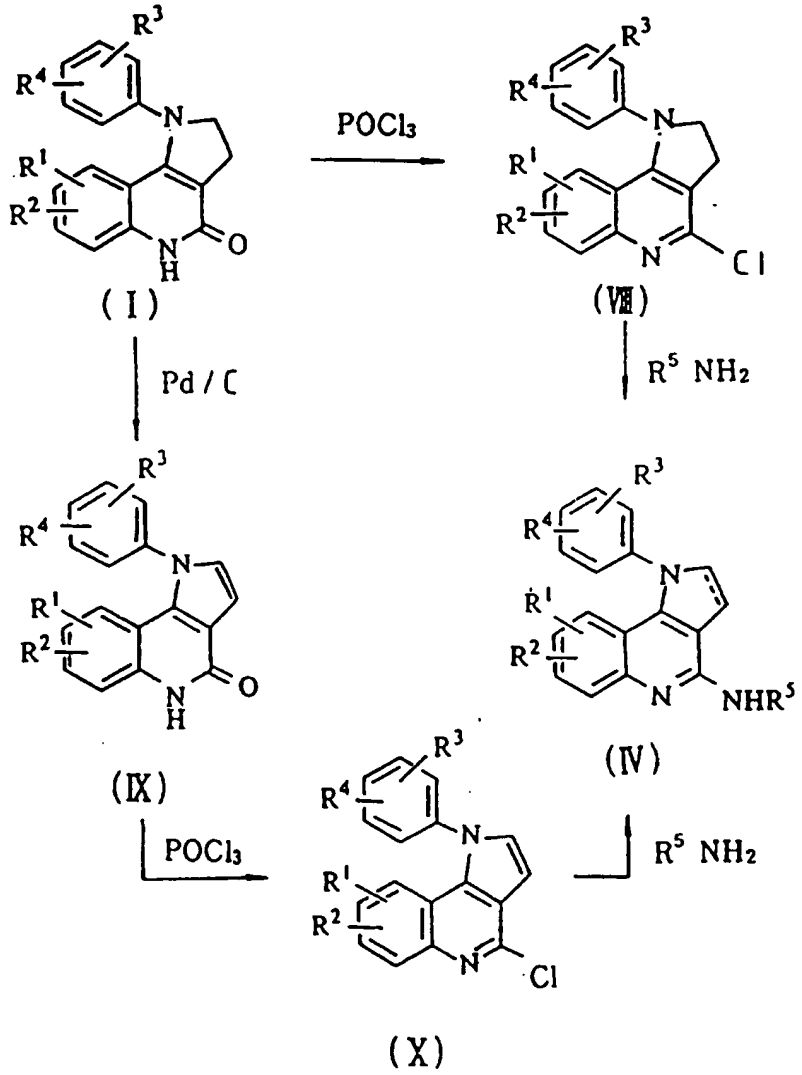
One to three equivalents of the anilines, as represented by structure III, is effective for preparation 4-oxopyrrolo[3,2-c]quinolines as represented by structure II.

Typical examples of the 1-aryl-4-oxopyrrolo[3,2-c]quinoline derivatives as represented by structure I according to the present invention are shown in table 1, as follows:

<table 1>

No.	R^1/R^2	R^3/R^4
1	H	2-CH_3
2	H	2-OCH_3
3	H	2-CH_3/4-OCH_3
4	6-CH_3	H
5	6-CH_3	2-CH_3
6	6-CH_3	2-OCH_3
7	6-CH_3	2-CH_3/4-OCH_3
8	6-CH_3	2-CH_3/4-OH
9	6-CH_3	2-CH_3/4-F
10	6-CH_3	2-CH_3/4-CH_3
11	6-CH_3	2-CH_2CH_3
12	6-OCH_3	H
13	6-OCH_3	2-CH_3
14	6-OCH_3	2-OCH_3
15	6-OCH_3	2-CH_3/4-OCH_3
16	6-OCH_3	2-CH_3/4-OH
17	6-OCH_3	2-CH_3/4-F
18	6-OCH_3	2-CH_3/6-CH_3
19	6-OCH_3	3-CH_3
20	6-F	2-CH_3
21	6-F	2-OCH_3
22	6-CF_3	2-CH_3
23	6-OCF_3	H
24	6-OCF_3	2-CH_3
25	6-OCF_3	2-OCH_3
26	6-OCF_3	2-CH_3/4-OCH_3
27	6-OCF_3	2-CH_3/4-OH
28	6-OCF_3	2-CH_3/4-F
29	6-OCF_3	2-CH_3/6-CH3
30	6-OCH_2CF_3	2-CH_3
31	6-OCH_2CF_3	2-CH_3/4-OH
32	6-SCH_3	2-CH_3
33	6-CH_3/8-OCH_3	2-CH_3
34	6-CH_3/8-F	2-OCH_3
35	6-OCH_3/7-F	2-CH_3
36	6-OH	2-CH_3
37	6-OCF_3/8-OCH3	2-CH_3
38	6-OCH_2CH_2OH	2-CH_3
39	6-CH_2OH	2-CH_3
40	6-CH(OH)CH_3	2-CH_3

The 1-aryl-4-oxopyrrolo[3,2-c]quinoline derivatives I which is prepared as above can be used to prepare the compound IV as a reversible inhibitor of the gastric acid secretion through the publicly known method (J. Med. Chem., 1992, 35, 1845)



While the invention has been described by reference to specific examples chosen for purposes of illustration, it should be apparent that the present invention be not limited by the specific disclosure herein and numerous modifications could be made thereto by those skilled in the art without departing from the basic concept and scope of the invention.

<Example 1>

Preparation of 1-(2-methylphenyl)-4-oxo-6-methyl-2,3,4,5-tetrahydropyrrolo[3,2-c]quinoline

4-Oxo-6-methyl-2,3-dihydrofuro[3,2-c]quinoline (201 mg, 1.0 mmol) was dissolved in 10ml of diethylene glycol in a pressure tube and 2-methylaniline (267μl, 2.5mmol) was added under nitrogen. The reaction mixture was heated at 250°C for 15 hours. The reaction mixture was diluted with 20ml of saline and the aqueous layer was extracted with methylene chloride (15ml x 3). After washing with water (15ml x 3), the organic layer was dried with anhydrous magnesium sulfate and filtered, and concentrated under reduced pressure. The residue was purified with ethyl acetate as eluent by silica gel chromatography to obtain 237mg of a desired compound as solid in 82% of yield.

mp: 171-173°C

^{1}H NMR($CDCl_3$, 200MHz): δ 2.31(s, 3H), 2.44(s, 3H), 3.05-3.38(m, 2H), 3.76(q, 1H), 4.05-4.23(m, 1H), 6.55-6.75(m, 2H), 7.05-7.39(m, 5H), 8.74(brs, 1H)

m/e: 290(M^+)

<Example 2>

Preparation of 1-(2-methoxyphenyl)-4-oxo-6-methyl-2,3,4,5-tetrahydropyrrolo[3,2-c]quinoline

4-Oxo-6-methyl-2,3-dihydrofuro[3,2-c]quinoline (201mg, 1.0mmol) was dissolved in 10ml of diethylene glycol and 2-methoxyaniline (282μl, 2.5mmol) was added under nitrogen. The reaction mixture was heated at 250°C for 15 hours. The reaction mixture was diluted with 20ml of salt water and the aqueous layer was extracted with methylene chloride (15ml x 3). After washing with water (15ml x 3), the organic layer was dried by anhydrous magnesium sulfate and filtered, and concentrated under reduced pressure. The residue was purified with ethyl acetate as eluent by silica gel chromatography to obtain 242mg of desired compound as solid in 79% of yield.

mp: 193-195°C

^{1}H NMR($CDCl_3$, 200MHz): δ 2.39(s, 3H), 3.15-3.29

(m, 2H), 3.74(s, 3H), 3.68-3.85(m, 1H), 4.05-4.27(m, 1H), 6.05-7.40(m, 7H), 8.41(brs, 1H)

m/e: 360(M^+)

<Example 3>

Preparation of 1-(2-methyl-4-methoxyphenyl)-4-oxo-6-methyl-2,3,4,5-tetrahydropyrrolo[3,2-c]quinoline

4-Oxo-6-methyl-2,3-dihydropuro[3,2-c]quinoline (201mg, 1.0mmol) was dissolved in 10ml of diethylene glycol in a pressure tube and 2-methyl-4-methoxyaniline (322μl, 2.5mmol) was added under nitrogen. The reaction mixture was heated at 250°C for 15 hours. The reaction mixture was diluted with 20ml of salt water and the aqueous layer was extracted with methylene chloride (15ml x 3). After washing with water (15ml x 3), the organic layer was dried by anhydrous magnesium sulfate and filtered, and concentrated under reduced pressure. The residue was purified with ethyl acetate as eluent by silica gel chromatography to obtain 272mg of desired compound as solid in 85% of yield.

mp: 210-213°C

^{1}H NMR($CDCl_3$, 200MHz): δ 2.38(s, 3H), 2.41(s, 3H), 3.07-3.37(m, 2H), 3.68-3.92(m, 1H), 3.83(s, 3H), 4.01-4.18(m, 1H), 6.57-6.89(m, 4H), 7.03-7.29(s, 32H),

8.41(brs, 1H)

m/e: 320(M^+)

<Example 4>

Preparation of 1-(2-methyl-4-hydroxyphenyl)-4-oxo-6-methyl-2,3,4,5-tetrahydropyrrolo[3,2-c]quinoline

4-Oxo-6-methyl-2,3-dihydrofuro[3,2-c]quinoline (201mg, 1.0mmol) was dissolved in 10ml of diethylene glycol in a pressure tube and 4-amino-m-cresol (308mg, 2.5mmol) was added under nitrogen. The reaction mixture was heated at 250°C for 15 hours. The reaction mixture was diluted in 20ml of salt water and the aqueous layer was extracted by methylene chloride (15ml x 3). After washing with water (15ml x 3), the organic layer was dried by anhydrous magnesium sulfate and filtered, and concentrated under reduced pressure. The residue was purified with ethyl acetate as eluent by silica gel chromatography to obtain 210mg of desired compound as solid in 81% of yield.

mp: 244-246°C

^{1}H NMR($CDCl_3$, 200MHz): δ 2.18(s, 3H), 2.39(s, 3H), 3.05-3.39(m, 2H), 3.74-3.94(m, 1H), 3.98-4.17(m, 1H), 6.63-7.27(m, 6H), 8.55(brs, 1H), 9.49(brs, 1H)

m/e: 306(M^+)

<Example 5>

Preparation of 1-(phenyl)-4-oxo-6-methoxy-2,3,4,5-tetrahydropyrrolo[3,2-c]quinoline

4-Oxo-6-methoxy-2,3-dihydrofuro[3,2-c]quinoline (217mg, 1.0mmol) was dissolved in 7ml of phenol and aniline (228μl, 2.5mmol) was added under nitrogen. The reaction mixture was heated at 190°C for 15 hours. The reaction mixture was diluted with 20ml of salt water and the aqueous layer was extracted with methylene chloride (15ml x 3). After washing with water (15ml x 3), the organic layer was dried by anhydrous magnesium surface and filtered, and concentrated under reduced pressure. The residue was purified with ethyl acetate as eluent by silica gel chromatography to obtain 240mg of desired compound as solid in 83% of yield.

mp: 75-77°C

^{1}H NMR($CDCl_3$, 200MHz): δ 3.12(t, J=9.2Hz, 2H), 3.89(s, 3H), 4.03(t, J=9.5Hz, 2H), 6.50(d, J=7.8Hz, 1H), 6.71-7.33(m, 7H), 8.91(brs, 1H)

m/e: 292(M^+)

<Example 6>

Preparation of 1-(2-methylphenyl)-4-oxo-6-methoxy-2,3,4,5-tetrahydropyrrolo[3,2-c]quinoline

4-Oxo-6-methoxy-2,3-dihydrofuro[3,2-c]quinoline (217mg, 1.0mmol) was dissolved in 10ml of diethylene glycol in a pressure tube and 2-methylaniline (267μl, 2.5mmol) was added under nitrogen. The reaction mixture was heated at 250°C for 15 hours. The reaction mixture was diluted with 20ml of salt water and the aqueous layer was extracted with methylene chloride (15ml x 3). After washing with water (15ml x 3), the organic layer was dried by anhydrous magnesium sulfate and filtered, amd concentrated under reduced pressure. The residue was purified with ethyl acetate as eluent by silica gel chromatography to obtain 235mg of desired compound as solid in 77% of yield.

mp: 166-168°C

^{1}H NMR($CDCl_3$, 200MHz): δ 2.34(s, 3H), 3.11-3.41 (m, 2H), 3.72-3.91(m, 1H), 3.97(s, 3H), 4.06-4.28(m, 1H), 6.28(d, J=7.9Hz, 1H), 6.73(d, J=8.2Hz, 1H), 6.82(d, J=7.9Hz, 1H), 7.05-7.42(m, 4H), 8.91(brs, 1H)

m/e: 306(M^+)

J=8.2Hz, 1H), 6.82(d, J=7.9Hz, 1H), 7.05-7.42(m, 4H), 8.91(brs, 1H)

m/e: 306(M^+)

<Example 7>

Preparation of 1-(2-methoxyphenyl)-4-oxo-6-methoxy-2,3,4,5-tetrahydropyrrolo[3,2-c]quinoline

4-Oxo-6-methoxy-2,3-dihydrofuro[3,2-c]quinoline (217mg, 1.0mmol) was dissolved in 10ml of diethylene glycol in a pressure tube and of 2-methylaniline (282μl, 2.5mmol) was added under nitrogen. The reaction mixture was heated at 250°C for 15 hours. The reaction mixture was diluted with 20ml of salt water and the aqueous layer was extracted with methylene chloride (15ml x 3). After layer with water (15ml x 3), the organic layer was dried with anhydrous magnesium sulfate and filtrated to be concentrated under reduced pressure. The residue was purified with ethyl acetate as a development solution according to silica gel chromatography to obtain 260mg of desired compound as solid in 81% of yield.

mp: 185-188°C

^{1}H NMR($CDCl_3$, 200MHz): δ 3.18(t, J=9.2Hz, 2H), 3.70-4.21(m, 2H), 3.73(s, 3H), 6.44(d, J=8.2Hz, 1H),

6.67-7.34(m, 6H), 8.87(brs, 1H)

m/e: 322(M^+)

<Example 8>

Preparation of 1-(2-methyl-4-methoxyphenyl)-4-oxo-6-methoxy-2,3,4,5-tetrahydropyrrolo[3,2-c]quinoline

4-Oxo-6-methoxy-2,3-dihydrofuro[3,2-c]quinoline (217mg, 1.0mmol) was dissolved in 10ml of ethylene glycol and 4-methoxy-2-methylaniline (322μl, 2.5mmol) was added under nitrogen. The reaction mixture was heated at 210°C for 15 hours. The reaction mixture was diluted with 20ml of salt water and the aqueous layer was extracted with methylene chloride (15ml x 3). After washing with water (15ml x 3), the organic layer was dried by anhydrous magnesium sulfate and filtered, and concentrated under reduced pressure. The residue was purified with ethyl acetate as eluent by silica gel chromatography to obtain 270mg of desired compound as solid in 81% of yield.

mp: 188-191°C

^{1}H NMR($CDCl_3$, 200MHz): δ 2.23(s, 3H), 3.05-3.35(m, 2H), 3.80(s, 3H), 3.88(s, 3H), 3.80-4.11(m, 2H), 6.27(dd, J=8.1Hz, J2=1.1Hz, 1H),

6.65-6.85(m, 4H), 7.04(d, J=8.6Hz, 1H), 8.83(brs, 1H)

m/e: 336(M^+)

<Example 9>

Preparation of 1-(2-methyl-4-fluorphenyl)-4-oxo-6-methoxy-2,3,4,5-tetrahydropyrrolo[3,2-c]quinoline

4-Oxo-6-methoxy-2,3-dihydrofuro[3,2-c]quinoline (217mg, 1.0mmol) was dissolved in 10ml of diethylene glycol in a pressure tube and (278μl, 2.5mmol) of 4-fluor-2-methylaniline (278μl, 2.5mmol) was added under nitrogen. The reaction mixture was heated at 250°C for 15 hours. The reaction mixture was diluted with 20ml of salt water and the aqueous layer was extracted with methylene chloride (15ml x 3). After washing with water (15ml x 3), the organic layer was dried by anhydrous magnesium sulfate and filtered, and concentrated under reduced pressure.

The residue was purified with ethyl acetate as eluent according to silica gel chromatography to obtain 256mg of desired compound as solid in 79% of yield.

mp: 195-198°C

^1H NMR($CDCl_3$, 200MHz): δ 2.28(s, 3H), 3.01-3.35(m, 2H), 3.51-3.82(m, 1H), 3.89(s, 3H),

3.88-4.15(m, 1H), 6.21(d, J=8.1Hz, 1H), 6.65-7.14(m, 5H), 8.89(brs, 1H)

m/e: 324(M^+)

<Example 10>

Preparation of 1-(3-methylphenyl)-4-oxo-6-methoxy-2,3,4,5-tetrahydropyrrolo[3,2-c]quinoline

4-Oxo-6-methoxy-2,3-dihydrofuro[3,2-c]quinoline (217mg, 1.0mmol) was dissolved in 7ml of phenol in a pressure tube and 3-methylaniline (268μl, 2.5mmol) was added under nitrogen. The reaction mixture was heated at 190°C for 15 hours. The reaction mixture was diluted with 20ml of salt water and the aqueous layer was extracted with methylene chloride (15ml x 3). After washing with water (15ml x 3), the organic layer was dried by anhydrous magnesium sulfate and filtered, and concentrated under reduced pressure. The residue was purified with ethyl acetate as eluent by silica gel chromatography to obtain 230mg of desired compound as solid in 76% of yield.

mp: 155-157°C

^1H NMR($CDCl_3$, 200MHz): δ 2.32(s, 3H), 3.16(t, J=9.2Hz, 2H), 3.92(s, 3H), 4.06(t, J=9.5Hz, 2H), 6.56-7.18(m, 6H), 7.24(t, J=6.4Hz, 1H), 8.91(brs,

1H)

m/e: 306(M^+)

<Example 11>

Preparation of 1-(2-methylphenyl)-4-oxo-6-trifluormethoxy-2,3,4,5-tetrahydropyrrolo[3,2-c]quinoline

4-Oxo-6-trifluormethoxy-2,3-dihydrofuro[3,2-c]quinoline (272mg, 1.0mmol) was dissolved in 10ml of diethylene glycol and 2-methylaniline (267μl, 1.0mmol) was added under nitrogen. The reaction mixture was heated at 250°C for 15 hours. The reaction mixture was diluted with 20ml of salt water and the aqueous layer was extracted with methylene chloride (15ml x 3). After washing with water (15ml x 3), the organic layer was dried by anhydrous magnesium sulfate and filtered, and concentrated under reduced pressure. The residue was purified with ethyl acetate as eluent by silica gel chromatography to obtain 298mg of desired compound as solid in 83% of yield.

mp: 153-156°C

^{1}H NMR($CDCl_3$, 200MHz): δ 2.31(s, 3H), 3.10-3.37(m, 2H), 3.79(q, J=10.2Hz, 1H), 4.07-4.21(m,

1H), 6.58(d, J=8.1Hz, 1H), 6.73(t, J=8.3Hz, 1H), 7.09-7.36(m, 5H), 8.71(brs, 1H)

m/e: 361(M^+)

<Example 12>

Preparation of 1-(2-methoxyphenyl)-4-oxo-6-trifluormethoxy-2,3,4,5-tetrahydropyrrolo[3,2-c]quinoline

4-Oxo-6-trifluormethoxy-2,3-dihydrofuro[3,2-c]quinoline (272mg, 1.0mmol) was dissolved in 10ml of ethylene glycol in a pressure tube and 2-methoxyaniline (282μl, 1.0mmol) was added under nitrogen. The reaction mixture was heated at 210°C for 15 hours. The reaction mixture was diluted with 20ml of salt water and the aqueous layer was extracted with methylene chloride (15ml x 3). After washing with water (15ml x 3), the organic layer was dried by anhydrous magnesium sulfate and filtered, and concentrated under reduced pressure.

The residue was purified with ethyl acetate as eluent by silica gel chromatography to obtain 286mg of desired compound as solid in 76% of yield.

mp: 171-173°C

^{1}H NMR($CDCl_3$, 200MHz): δ 3.18-3.31(m,

2H), 3.76(s, 3H), 3.75-3.95(m, 1H), 4.05-4.27(m, 1H), 6.75-7.48(m, 7H), 8.83(brs, 1H)

m/e: 377(M^+)

<Example 13>

1) Preparation of 1-(4-methoxy-2-methylphenyl)-4-chloro-6-methyl-2,3-dihydropyrrolo[3,2-c]quinoline

1-(4-methoxy-2-methylphenyl)-4-oxo-6-methyl-2,3,4,5-tetrahydropyrrolo[3,2-c]quinoline (1.0g, 3.1mmol) was dissolved in 10ml of phosphoryl chloride ($POCl_3$) and heated for 2 hours. The reaction mixture was stirred at room temperature for 30 minutes after cooling and addition of ice water. The reaction mixture was extracted with methylene chloride (20ml x 3). After washing with water (15ml x 3), the organic layer was dried by anhydrous magnesium sulfate and filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to obtain 786mg of desired compound as an oil in 75% of yield.

^1H NMR($CDCl_3$, 200MHz): δ 2.24(s, 3H), 2.65(s, 3H), 3.05-3.35(m, 2H), 3.85(s, 3H), 3.80-4.11(m, 2H), 6.27(dd, J_1=8.1Hz, J_2=1.1Hz, 1H), 6.65-6.89(m, 4H),

7.05(d, J=8.4Hz, 1H)

m/e: 338(M^+)

2) Preparation of 1-(4-methoxy-2-methylamino)-6-methyl-2,3-dihydropyrrolo[3,2-c]quinoline (IV)

1-(4-methoxy-2-methyl phenyl)-4-chloro-6-methyl-2,3-dihydropyrrolo [3,2-c]quinoline (496mg, 1.2mmol) was dissolved in 10ml of ethyl alcohol and 5ml of 40% aqueous methylamine was added. The reaction mixture was heated at 170°C for 20 hours in a pressure tube and solvent was distilled under reduced pressure. The reaction mixture was diluted with 20ml of methylene chloride. After washing with water (15ml x 3), the organic layer was dried by anhydrous magnesium sulfate and filtered, and concentrated under reduced pressure.

The residue was purified by silica gel chromatography to obtain 324mg of desired compound in 81% of yield.

^1H NMR($CDCl_3$, 200MHz): δ 2.27(s, 3H), 2.64(s, 3H), 2.91-3.20(m, 2H), 3.11(d, 3H), 3.65-3.82(m, 1H), 3.81(s, 3H), 4.03-4.21(m, 2H), 6.68-6.81(m, 3H), 6.83-6.90(m, 2H), 7.20-7.31(m, 1H)

m/e: 333(M^+)

<Example 14>

1) Preparation of 1-(2-methylphenyl)-4-oxo-6-methyl-4,5-dihydropyrrolo[3,2-c]quinoline(IX)

1-(2-methylphenyl)-4-oxo-6-methyl-2,3,4,5-tetrahydropyrrolo[3,2-c]quinoline (290mg, 1.0mmol) was dissolved in 20ml of diphenyl ether and 40mg of 5% palladium/carbon was added. The reaction mixture was heated for 4 hours. The reaction mixture was cooled to the room temperature and directly purified by silica gel chromatography to obtain 245mg of desired compound as solid in 85% of yield.

mp:224-227°C

^{1}H NMR($CDCl_3$, 200MHz): δ 1.93(s, 3H), 2.81(s, 3H), 6.93-7.02(m, 2H), 7.15-7.63(m, 7H), 8.56(bra, 1H)

m/e: 288(M^+)

2) Preparation of 1-(2-methylphenyl)-4-chloro-6-methylpyrrolo[3,2-c]quinoline (X)

1-(2-methylphenyl)-4-oxo-6-methyl-4,5-dihydropyrrolo[3,2-c]quinoline (1.16g, 4.0mmol) was dissolved in 10ml of phosphoryl chloride ($POCl_3$) and heated for 2 hours. The reaction mixture was stirred at room temperature for 30 minutes after cooling and

5H)

m/e: 306(M^+)

3) preparation of 1-(2-methylphenyl)-4-[(2-hydroxyethyl)amino]-6-methylpyrrolo[3,2-c]quinoline (III)

1-(2-methylphenyl)-4-chloro-6-methylpyrrolo [3,2-c]quinoline (306mg, 1.0mmol) was dissolved in 10ml of ethanolamine in a pressure tube and heated at 150°C for 3 hours. After removal of the reaction solvent under reduced pressure and diluted in 20ml of methylene chloride, the residue was dried by anhydrous magnesium sulfate and filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to obtain 236mg of desired compound as solid in 72% of yield.

mp: 187-189°C

^{1}H NMR($CDCl_3$, 200MHz): δ 1.93(s, 3H), 2.69(s, 3H), 3.91-3.99(m, 4H), 5.61(bra, 1H), 6.67-7.01(m, 5H), 7.25-7.52(m, 5H)

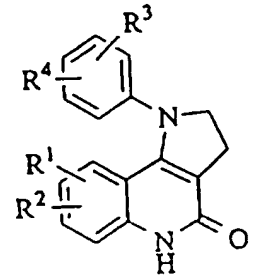
m/e: 331(M^+)

Effect of the invention

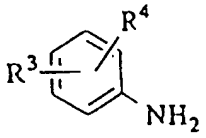
As apparent from the above examples, the process for preparing 1-aryl-4-oxopyrrolo[3,2-c] quinoline derivatives I according to the present invention adopts reagents of low cost under mild reaction conditions and the compound I may be prepared from the compound II in a single step. Especially, the preparation process according to the present invention can introduce various substituents such as R^1, R^2, R^3 and R_4 which have not been introduced in the prior art. Therefore, according to the present process, the compound IV which is a reversible inhibitor of the gastric acid secretion and has various substituents may be prepared safely and economically in high yield from the 1-aryl-4-oxopyrrolo[3,2-c]quinoline derivatives.

What is claimed is:

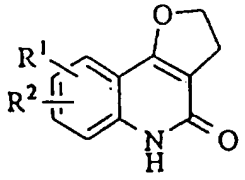
1. A process for preparing 1-aryl-4-oxopyrrolo [3,2-c]quinoline derivatives as represented by formula I, by reaction of 4-oxofuro[3,2-c]quinoline compounds as represented by formula II with anilines as represented by formula III:



(I)



(III)



(II)

wherein, R^1 may be same or different from R^2 which are respectively hydrogen, lower alkyl group of C_1-C_4, lower alkoxy group of C_1-C_4, lower alkylthio group of C_1-C_4, lower haloalkoxy group of C_1-C_4, trifluoromethyl group, hydroxyalkoxy group of C_1-C_4, halogen, or hydroxy group; and

R^3 may same or different from R^4 which are

halogen, or hydroxy group; and

R^3 may same or different from R^4 which are respectively hydrogen, lower alkyl group of C_1-C_4, lower alkoxy group of C_1-C_4, lower alkylthio group of C_1-C_4 lower haloalkyl group of C_1-C_4, trifluoromethyl group, hydroxy group, amino group, or halogen.

2. The process as claimed in claim 1, wherein R^1, R^2, R^3 and R^4 are same or different from each other and to be respectively hydrogen, methyl or methoxy.

3. The process as claimed in claim 1, wherein R^1, R^2, R^3 and R^4 are same or different from each other and to be respectively methyl, hydroxy or fluoro.

4. The process as claimed in claim 1, wherein R^1, and R^2 are respectively hydrogen or hydroxyalkoxy group, and R^3 and R^4 are same or different from each other and to be respectively hydrogen, methyl or methoxy.

5. The process as claimed in claim 1, wherein R^1, and R^2 are respectively hydrogen or hydroxyalkoxy group, and R^3 and R^4 are same or different from each other and to be respectively methyl, hydroxy or fluoro.

the reaction solvent is selected from dimethyl formamide, dimethylsulfoxide, diphenyl ether, xylene, butyl alcohol, phenol, ethylene glycol, diethylene glycol, triethylene glycol, polyetylene glycol, and ethylene glycol monomethyl ether.

7. The process as claimed in claim 1, wherein the reaction temperature is 70-300°C.

8. The process as claimed in claim 1, wherein the amount of the aniline compounds is used 1-3 equivalents for 4-oxofuro[3,2-c] quinoline compounds.

9. A process for preparing the compound as represented by formula IV by reacting 4-oxofuro[3,2-c] quinoline compounds as represented by formula II with aniline compounds as represented by formula III in a reaction solvent through a single step to obtain a compound as represented by formula I, adding $POCl_3$ to the compound I to obtain compound as represented by formula VIII, and adding alkylamine to the compound VIII.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 97/00074

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 471/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 471/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chemical Abstracts

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: DARC, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 307 078 A1 (SMITHKLINE BECKMAN) 15 March 1989 (15.03.89), example 9; formula IV; page 6, lines 4-20 (formulas V,VI) (cited in the application).	1-8
A	US 5 420 135 A (BROWN) 30 May 1995 (30.05.95), formula IV (cited in the application).	1
A	Chemical Abstracts, Vol.100, No.5, 30 January 1984 (Columbus, Ohio, USA), page 443, column 1, abstract No.34442u, EIDEN, F. et al.:"Studies on pyran derivatives. Part 97. Cyclization of α-(2-mercaptobenzoyl)- and α-(2-aminobenzoyl)lactams; synthesis of benzothiopyrano[4,3-b]pyrrolinones and pyrrolino- or tetrahydropyridino[3,2-c]quinolinones", & Arch. Pharm. (Weinheim, Ger.) 1983, 316(11), 897-907 (Ger).	1-8
A	Chemical Abstracts, Vol.112, No.7, 12 February 1990 (Columbus, Ohio, USA), page 14, column 1, abstract No.48250q, BROWN, T.H. et al.:"Reversible inhibitors of the gastric (H+/K+)-ATPase. 1. 1-Aryl-4-methyl=	1-8

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 June 1997 (16.06.97)	23 July 1997 (23.07.97)

Name and mailing address of the ISA/ AT	Authorized officer
AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna	Hammer
Facsimile No. 1/53424/535	Telephone No. 1/53424/374

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 97/00074

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	pyrrolo[3,2-c]quinolines as conformationally restrained analogs of 4-(arylamino)quinolines", & J. Med. Chem. 1990, 33(2), 527-33 (Eng). (cited in the application).	
A	Chemical Abstracts, Vol.116, No.25, 22 June 1992 (Columbus, Ohio, USA), page 779, column 2, abstract No.255506a, BROWN, T.H. et al.:"Reversible inhibitors of the gastric (H+/K+)-ATPase. 2. 1-Arylpyrrolo= [3,2-c]quinolines: effect of the 4-substituent", & J. Med. Chem. 1992, 35(10), 1845-52 (Eng).	1-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 97/00074

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

A: Process for preparing 1-Aryl-4-oxo-pyrrolo[3,2-c] quinoline Derivatives (claims 1-8)
B: Process for preparing 1-Aryl-4-(substituted)amino-pyrrolo [3,2-c]-quinoline Derivatives (claim 9)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-8

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 97/00074

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
EP A1 307078	15-03-89	AT E 79880	15-09-92
		AU A1 19200/88	27-01-89
		DE C0 3874056	01-10-92
		DE T2 3874056	07-01-93
		DK A0 4144/88	22-07-88
		DK A 4144/88	25-01-89
		EP B1 307078	26-08-92
		GB A0 8717644	03-09-87
		JP A2 1040482	10-02-89
		PT A 88033	30-06-89
		PT B 88033	31-03-95
		US A 5051508	24-09-91
		ZA A 8805311	26-07-89
US A 5420135	30-05-95	EP A2 441036	14-08-91
		EP A3 441036	26-02-92
		GB A0 8928281	21-02-90
		JP A2 7215973	15-08-95